REMARKS/ARGUMENTS

Upon entry of the amendment, claims 1, 3, 5-7, 13-21, 24-27, 28-29, and 30-36 will be pending in this application and presented for examination. Claim 21 has been amended. Support for the amendments to claim 21 is found, for example, in pending claim 1. Claims 22-23 have been canceled without prejudice or disclaimer. New claims 28 and 29 are added and find support from the canceled claims. New claims 30-36 are added and find support in claims 1, 5, 6, 7, 13-15, respectively. Further support for claim 30 is found at the bottom of page 17 to the top of page 18. No new matter has been entered with the foregoing amendments and newly added claims. Reconsideration is respectfully requested.

I. FORMALITIES

At the outset, Applicants and their undersigned representative wish to thank Examiners Young and Jones for the personal interview held on December 15, 2008. During this interview, a number of issues were clarified which have helped Applicants more clearly understand the Examiner's position and to present the below arguments to overcome the rejections. Applicants thank Examiners Young and Jones for their time and the courtesy of extending the personal interview.

II. THE INVENTION

The present invention relates *inter alia*, to a timed-release compression-coated formulation. Timed-release means, for example, that after a specific lag time, the active ingredient from the pharmaceutical preparation is released (*see*, Figure 1 of the specification). In the present invention, timed-release is achieved by the specific formulation of the core tablet and outer layer. The core tablet comprises an active ingredient and a freely erodible filler, wherein the freely erodible filler is 1 or 2 or more selected from the group of malic acid, citric acid, tartaric acid, polyethylene glycol, sucrose, and lactulose, and an outer layer wherein the outer layer is made from at least one type of polyethylene oxide and polyethylene glycol. The outer layer does not contain a drug.

III. DOUBLE PATENTING REJECTION

The Examiner has rejected claims 1, 3, 5-7 and 13-26 under the judicially created doctrine of obviousness-type double patenting as allegedly being obvious over claims 1, 3, 5-7 and 13-26 of co-pending U.S. Patent Application No. 11/463,570 in view of U.S. Patent No. 6,235,311 (Ullah *et al.*).

In response, Applicants submit herewith a terminal disclaimer which obviates the double patenting rejection. Accordingly, Applicants respectfully request that the rejection of the claims be withdrawn.

IV. FIRST REJECTION UNDER 35 U.S.C §103(a)

The Examiner has rejected claims 1, 7, 14-17, 21, 22, 24, 25 and 27 under 35 U.S.C. § 103(a) as allegedly being obvious over U.S. Patent No. 6,277,409 ("Luber *et al.*"). In response, Applicants respectfully traverse the rejection.

A claim is considered obvious "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains" (35 USC § 103(a)). The Supreme Court in *KSR International Co. v. Teleflex Inc.*, 550 U.S. ___, ___, 82 USPQ2d 1385, 1395-97 (2007) identified a number of rationales to support a conclusion of obviousness which are consistent with the proper "functional approach" to the determination of obviousness as laid down in *Graham.* The key to supporting any rejection under 35 U.S.C. § 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. The Supreme Court in *KSR* noted that the analysis supporting a rejection under 35 U.S.C. § 103 should be made explicit. One of the rationales addressed by the court in *KSR* supports a finding of obviousness when the prior art reference (or combination of references) (1) teaches or suggests the claim elements; (2) provides some suggestion or motivation to combine the references; and (3) provides a reasonable expectation of success (MPEP § 2143).

During the interview, the Examiner agreed to reconsider Luber *et al.* (US Patent No. 6,277,409) in view of our discussion. Again, Luber *et al.* teach a protective molten wax or thermoplastic material, which makes a hard outer layer.

In column 2, lines 5-10, Luber *et al.* state:

> [a]pplication of the protective coating according to the invention stabilizes the friability of the tablet. It also *provides a water-resistant barrier* for the tablet core. This is especially advantageous when its is desired to use conventional outer coatings on the tablet, which can erode the tablet core. By application of such outer coatings over the protective coating, the integrity of the tablet core is preserved. [Emphasis added].

The Luber *et al.* technology is completely different technology than the instant invention. The protective *molten wax* and thermoplastic materials of Luber *et al.*, which make a hard outer layer (up to 15 kp/cm^2) for the tablet, are in no way similar to the present invention. The process of Luber *et al.* makes these materials much different than the present invention. In fact, the waxy coating of Luber *et al.* prevents erosion (*e.g.*, shelf-life) of the inner core. Luber *et al.* teach at column 4, lines 14-19:

> Advantageously, the protective coating provides an impact resistant and water resistant cover of the tablet core. This stabilizes the friability of the tablet, and in addition *prevents erosion* of the tablet core by any outer coatings present on the tablet, which are of a relatively hydrophilic nature. [Emphasis added].

In the instant invention, the outer layer absorbs water and erodes the inner core. In the present case, as the hydrophilic base of the outer layer absorbs water, a hydrogel forms in order to retain the water, and the water in the tablet penetrates into the inner layer eroding the filler (e.g., 1 or 2 or more selected from the group consisting of malic acid, citric acid, tartaric acid, polyethylene glycol, sucrose, and lactulose) such that the inner core substantially becomes a solution state or suspension state. The outer layer must be able to absorb water.

The Luber *et al.* technology is similar to the technology as described in Guirgis *et al. Pham. Ind.* 63, No. 5 (2001) pages 499-507 (hereinafter "Guirgis," enclosed as the Exhibit).

The outer layer used in the hot melt processes of Guirgis are waxes (cetostearyl alcohol and glyceryl behenate). When the tablets of Guirgis, which use molten waxes were compared to the direct compression tablets (similar to the present invention) "[t]tablets prepared by the hot melt techniques produced slower drug release than by direct compression." (see, page 504, left hand column, lines 19-21). "It was found that hot melt technology significantly extended release of theophylline from the resulting tablets compared to those manufactured by direct compression." (see, page 507, left hand column, lines 1-4).

The tablets of Luber *et al.* use a protective molten wax or thermoplastic material, which makes a hard outer layer. By the patentees own admission, this hard outer layer "stabilizes the friability of the tablet. It also *provides a water-resistant barrier* for the tablet core." (column 4, lines 16-17). As such, Luber *et al.* teach away from the present invention. In view of the above, Applicants request that the Examiner withdraw this rejection and send this application to issue.

V. SECOND REJECTION UNDER 35 U.S.C §103(a)

The Examiner has rejected claims 1, 3, 5-7, and 13-26 as allegedly being obvious over the combined disclosures of Luber *et al.,* in view of Sako *et al.,* (EP 0 661 045) and Taniguchi *et al.,* (EP 0 709 386). In response, Applicants respectfully traverse the rejection.

Again, the Luber *et al.* technology is completely different technology than the instant invention. The protective *molten wax* and thermoplastic materials of Luber *et al.*, which make a hard outer layer (up to 15 kp/cm^2) for the tablet, are in no way similar to the present invention. The process of Luber *et al.* makes these materials much different than the present invention. In fact, the waxy coating of Luber *et al.* prevents erosion (*e.g.*, shelf-life) of the inner core. Luber *et al.* teach at column 4, lines 14-19:

> Advantageously, the protective coating provides an impact resistant and water resistant cover of the tablet core. This stabilizes the friability of the tablet, and in addition *prevents erosion* of the tablet core by any outer coatings present on the tablet, which are of a relatively hydrophilic nature. [Emphasis added].

As discussed above, Luber *et al.* teach away from the present invention.

Sako *et al.* teach a tablet that contains a *single-layer*, *i.e.*, a homogeneous formulation which comprises a i) a drug, ii) an additive providing for the penetration of water in to the core of the preparation, and iii) a hydrogel-forming polymer. The tablet travels through the digestive system and the tablet is continuously eroded, thereby releasing the drug at every step along the way, from the upper digestive tract to the colon. The teaching of Sako *et al.* is much different than the current invention. Sako *et al.* do not teach or suggest an erodible core and outer layer as claimed. In the embodiments of the present invention, there is an inner core and an outer layer. At least two distinct layers are present. This is in clear contrast to the disclosure of Sako *et al.*, which is a *homogenous* sustained release tablet comprising i) an active agent; ii) an additive, e.g., a hydrophilic base; and iii) a hydrogel forming polymer.

Taniguchi *et al.* teach benzazepeine compounds and pharmaceutical compositions thereof. Taniguchi *et al.* disclose a list of general pharmaceutical ingredients that can be used to formulate a tablet composition comprising the benzazepeine compounds (*see*, page 27, lines 30-37).

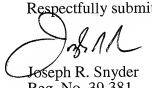
Luber *et al.*, Sako *et al.*, and Taniguchi *et al.*, alone or when combined, simply do not teach or suggest the specific combination of a core comprising the freely erodible filler for a drug that is 1 or 2 or more selected from the group consisting of malic acid, citric acid and tartaric acid, polyethylene glycol, sucrose, and lactulose, and the outer layer that is made from at least one type of polyethylene oxide, and polyethylene glycol. The combination of references do not teach the all the features of the claims. Accordingly, Applicants respectfully request that the rejection of the claims be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,



Joseph R. Snyder
Reg. No. 39,381

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel: 925-472-5000
Fax: 415-576-0300
Attachments
JS:js
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EXHIBIT

Hot Melt Technology

2nd Communication: Effect of Manufacturing Method on Tablet Characteristics[1)]

Heba Guirgis[a], Blanca Broegmann[b], and Adel Sakr[a]

Industrial Pharmacy Graduate Program, College of Pharmacy, University of Cincinnati[a], Cincinnati, Ohio (USA), and Mundipharma GmbH[b], Limburg (Germany)

Summary

A full factorial design has been implemented to study the characteristics of granules and tablets prepared by the hot melt technology using the high shear mixer/granulator (HSMG) and the fluid bed processor (FBP). The results were compared with those obtained by direct compression. Granules consisting of theophylline monohydrate and lactose granulated with polyvinylpyrrolidone solution were used as substrate. Hot melt excipients: cetostearyl alcohol (CSA, Lanette® O) and glyceryl behenate (GB) were evaluated using the three manufacturing techniques.

The tablets were compressed using a Korsch PH 106/DMS instrumented tablet machine. The resulting granules and tablets were examined using scanning electron microscopy (SEM) and were evaluated for their physical characteristics. In vitro dissolution tests were done using automated USP apparatus II, at a paddle speed of 50 rpm in 900 ml pH 6.0 phosphate buffer for 20 h. SEM micrographs showed that on applying the melt excipient to the granules in the HSMG, a process of granulation and deposition of the melt excipient takes place while in the FBP granule coating occurs. Experiments were carried out to investigate in depth the mechanism of granule formation and release patterns using hot melt technology.

It was found that using the same amount of melt excipient, direct compression was as successful as the high shear technique in modifying drug release in case of GB, and almost as the fluid bed technique in case of CSA.

Zusammenfassung

Hot melt-Technologie / 2. Mitteilung: Einfluß der Herstellungsmethode auf die Tabletteneigenschaften

In einem voll-faktoriellen Design wurden die Eigenschaften von mit Hot melt-Technologie und Zwangsmischer/-granulator hergestellten Granulaten und Tabletten untersucht. Die Resultate wurden mit denen verglichen, die mit Direktverpressung erzielt werden. Granulate bestehend aus Theophyllin-Monohydrat und Lactose, granuliert mit Polyvinylpyrrolidon-Lösung, wurden als Substrat verwendet. Die Heißschmelz-Exzipienten Cetylstearyl-Alkohol (Lanette® O) und Glycerylbehenat wurden in den drei Herstellungstechniken evaluiert.

Die Tabletten wurden auf einer mit Dehnungsstreifen instrumentierten Korsch PH 106/DMS verpreßt. Granulate und Tabletten wurden mit dem Rasterelektronenmikroskop untersucht und auf ihre physikalischen Eigenschaften geprüft. In-vitro-Dissolutionstests wurden mit dem automatisierten USP-Apparat Typ II bei einer Rührgeschwindigkeit von 50 U/min in 900 ml Phosphatpuffer mit pH 6,0 über 20 h durchgeführt. Rasterelektronenmikroskopische Aufnahmen zeigten, daß nach Anwendung des Schmelzexzipiens im Zwangsmischer/-granulator ein Granulationsprozeß und ein Sich-Niederschlagen des Schmelzexzipiens stattfindet, während es im Fließbett-Prozessor zu einer Umhüllung (coating) der Granula kommt. Weitere Versuche wurden angestellt, um die Mechanismen der Granulatbildung und der Freisetzungsmuster im Zusammenhang mit der Heißschmelz-Technologie im Detail zu klären.

Es wurde gefunden, daß beim Einsatz einer gleich großen Menge an Heißschmelz-Exzipiens die Direktverpressung zur Beeinflussung des Freisetzungsverhaltens so effektiv wie die Zwangsmisch-Technik bei Einsatz von Glycerylbehenat und nahezu so effektiv wie die Fließbett-Technik beim Einsatz von Cetylstearyl-Alkohol.

Key words

- Cetostearyl alcohol
- Glyceryl behenate
- Granulation, direct compression, fluid bed processing, high shear mixer
- Hot melt technology

Pharm. Ind. 63, 499–507 (2001)

1) 1st Communication with Part I and II see Pharm. Ind. 63, No. 3, pp. 297, and No. 4, pp. 395 (2001).

1. Introduction

Conventional coating techniques require the use of a solvent (aqueous or organic) that must be evaporated. Available coating agents are applied as solutions or dispersions and usually contain no more than 30 % solids. Hot melt coating techniques offer a solvent-free coating technique since the coating material is applied in its molten state. Also, as there is no solvent to evaporate, the processing times are much shorter than the current practices [1].

Coating trials have been successfully conducted utilizing the top-spray fluidized-bed coater for hot melt excipient application where the substrate is placed in a product container and is fluidized vigorously using heated air. The particles are accelerated upward past a nozzle that sprays the molten coating liquid. Exiting the spray zone, the product enters the expansion chamber, which is wider in diameter than the base of the product container. This allows the cooling particles to decelerate and fall back into the product container to continue cycling throughout the duration of spraying. Coating occurs as the atomized liquid droplets impact the particles, spread, and solidify. This process continues, with layers building up to the desired level of coating. This is followed by a final product stabilization or cooling step [2].

At present, there are few publications on the fluid bed hot melt technology. Among those is a study by Jozviakowski, Franz, and Jones [3], characterizing a hot melt fluid bed coating process for fine granules where tapped density, particle size and the dissolution responses were changed significantly by altering the coating parameters and were considered the relevant response variables for the study. Atomizing air pressure had the greatest effect on the relevant responses.

Jonchim et al. [1] evaluated the coating of drug-loaded sugar beads and granules with Compritol 888 ATO® (NF glyceryl behenate). They fouud that drug release was related to the quantity of wax coated.

Barthelemy et al. [4] found that the coating conditions, especially the temperature of the coating material, were of highest importance for the spreadability and consistency of the coating. Higher temperatures lead to better covering of the granules, in spite of their irregular surfaces.

Another method for applying hot melt excipients utilizes the high shear mixer where melt granulation is achieved by adding the binder in its molten form, or in powder form to the starting material followed by heating. The temperature is increased by a heating jacket or by heat of friction solely. Heating by a heating jacket might be possible in a laboratory scale mixer but might be inconvenient in production which may be due to the difficulty encountered in controlling the temperature of the heating jacket by water flow [5].

Schaefer, Holm and Kristensen [6] found that impeller speed and massing time were critical process variables in producing dense, rounded pellets with a narrow size distribution. The type and concentration of the melting binder polyethylene glycol affected the mean granule size, while size distribution was primarily controlled by impeller speed [7]. Evaluating the effect of lactose and particle size on melt pelletization, it was concluded that lactose yielded smaller pellets than those from lactose monohydrate [8]. A correlation between the power consumption and mean granule size was found.

Furthermore, Schaefer et al. [9] found that the highest impeller speed resulted in the largest and most rounded pellets. Apparatus variables were also evaluated [10].

Royce et al. [11] studied the melt granulation technique in Collette high shear Gral mixer. Heating by a heating jacket was done to increase the temperature of the blended ingredients in the bowl where the process of drying in wet granulation is replaced by cooling in the melt granulation process.

The focus of this study was to evaluate hot melt technology for the manufacture of modified release tablets, utilizing the high shear mixer/granulator and the fluid bed processor in comparison to direct compression.

2. Materials and equipment

2.1. Materials

Cetostearyl alcohol (CSA; Lanette® O), Brenntag Chemiepartner, Frankfurt (Germany); glyceryl behenate (GB: Compritol 888 ATO®), Gattefossé Holding, Saint-Priest Cedex (France); Lactose GK (Capsulac® 60 type EP D 20), Meggle, Wasserburg (Germany); magnesium stearate, Akcros Chemicals, Venlo (The Netherlands); microcrystalline cellulose (Avicel® PH-101, PH-200 and PH-301), FMC Corp.: Philadelphia, PA (USA); polyethylene glycol 4000 Schuppen (PEG® 4000 S DAB), Hoechst AG, Burgkirchen (Germany); polyvinylpyrrolidone (Kollidon® 25), BASF, Ludwigshafen (Germany); theophylline monohydrate powder, Knoll, Ludwigshafen (Germany).

2.2. Equipment

Automatic powder flow instrument, Pharma Test PTG, SITCO, Boundbrook, NJ (USA); cone mill GKM, Alexanderwerk, Remscheid (Germany); cube mixer, Erweka-Apparatebau GmbH, Heusenstamm (Germany); fluid bed processor, Glatt GPCG-3 with a GPCG-1 insert and Eco View, Glatt GmbH Systemtechnik, Dresden (Germany); hand micrometer, Starret dial hand micrometer, L. S. Starret Co., Athol, MA (USA); high shear mixer / granulator, Gral-10 and Gral-25, Machines Collette, Wommelgen/Antwerp (Belgium); humidity tester, Mettler-Toledo LP 16, Mettler-Toledo, Greifensee (Switzerland); oscillating granulator, Erweka AR 400, Erweka-Apparatebau GmbH, Heusenstamm (Germany); rotary tablet press, Korsch PH 106/DMS, Korsch Pressen, Berlin (Germany); scientific sieve shaker, CSC Scientific company Inc., Fairfax, VA (USA); spectrophotometer, Beckman DU-64, Beckman, München (Germany); tap density tester, Vankerkamp, Vankel Industries Inc., Edison, NJ (USA).

3. Methodology

A full factorial design was implemented to evaluate hot melt technology for the manufacture of modified release tablets in

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comparison to direct compression. Two hot melt techniques, utilizing the fluid bed processor and the high shear mixer-granulator, were studied.

Granules consisting of theophylline monohydrate and lactose granulated with polyvinylpyrrolidone solution were used as substrate. GB were evaluated for their use as modified release melt excipients when applied at 10 % w/w added to the substrate granules.

3.1. Substrate granule manufacture

The same methodology previously described in Part 1 of this publication was used [12]. Granules in the particle size range of 0.355–1.25 mm were separated and used as the substrate granules.

3.2. Hot melt granulation using the high shear mixer-granulator

The substrate granules were weighed and charged into the high shear mixer. A 1-kg batch was used.

3.2.1. Melt excipient preparation

The melt excipient was weighed in a glass beaker and heated on an electric heater till complete melting. The temperature of the melt excipient was maintained at a constant value of 110–115 °C. The amount of the melt excipient was 10 % w/w added to the substrate granules. The melt excipient was applied to the granules though a pre-warmed funnel placed at the liquid inlet of the high shear mixer.

3.3. Hot melt fluid bed technique

Formulations were prepared using the Glatt powder coater granulator (GPCG-3 with a GPCG-1 insert) top spray attachment. Fluidized bed coating conditions are listed in Table 1. These conditions were selected based on the melt excipients and substrate's properties.

3.4. Tablet compression

After application of the melt excipient, the granules were collected, cooled for 1 h delumped in an oscillating granulator fitted with a 1.6 mm sieve and finally, 1 % magnesium stearate was mixed with the granules for 3 min in a cube mixer.

Tablets were prepared using an instrumented Korsch PH106/DMS rotary tablet press using standard 10 mm flat beveled stations. Calculations were made so that each tablet contained 100 mg of anhydrous theophylline and were compressed at two different compression forces: 4–6 and 9–11 kN. The tablet weight was adjusted to 384.93 mg.

3.5. Tablet manufacture by direct compression

CSA was supplied by the manufacturer in the form of beads. In order to use it in a direct compression formula, it had to be milled. A 1.0 mm sieve fitted in an oscillating granulator was used for this purpose. The granulator was set at a very low speed to prevent melting resulting from heat generation. GB was used as received from the supplier as it was in the form of finely atomized powder.

The substrate granules were mixed with either the CSA or GB for 15 min in a cube mixer. Tablets were compressed in the same manner as mentioned in step 3.4.

Table 1: Conditions for fluid bed hot melt application.

Condition	Settings for CSA	Settings for GB
Exhaust air flap (%)	40–50	40–50
Set inlet air temperature (°C)	40 for equipment warm up, 25 during spraying	80 for equipment warm up, 75 during spraying
Product bed temperature (°C)	30	67
Atomizing air temperature (°C)	120	120
Atomizing air pressure (bar)	2.5	2.5
Nozzle position	2 (lower)	2 (lower)
Nozzle diameter (mm)	1.2	1.2
Spray rate (g/min)	14–15	11–12
Filter shake time (asynchronous) (s)	3	3
Filter shake intervals (s)	10	10

4. Granule evaluation

4.1. Flowability

An automatic powder flow instrument was used to measure the angle of repose. Samples were placed in the sample cup and leveled. The granules flowed through a 9.0 mm orifice from a standard height onto a flat horizontal surface. The angle of repose was calculated and displayed by the instrument and was reported in degrees. This test was repeated 3 times. The means and standard deviations are presented (Table 2).

4.2. Bulk and tapped density

The bulk density was determined by pouring a pre-weighed sample through a funnel from a standard height into a 100 ml graduated cylinder. The tapped density was determined using an automated tapped density apparatus by subjecting the graduated cylinder to 200 taps. The results were reported as weight/volume. This test was repeated twice. The means and standard deviations are presented (Table 2).

4.3. Scanning electron microscopy (SEM)

Scanning electron micrographs were taken for the melt excipient based granules produced by the different manufacturing techniques. The granules were gold sputtered using a sputter coater before they were loaded into the scanning electron microscope. A secondary electron detector was used.

5. Tablet evaluation

5.1. Weight variation

Ten tablets from each batch were weighed using a calibrated analytical balance. The weights were recorded in mg. The means and standard deviations are presented (Table 3).

5.2. Tablet thickness

The thickness of the tablets, previously tested for weight variation, was measured using a calibrated portable dial hand micrometer. Values were recorded in mm. The means and standard deviations are presented (Table 3).

5.3. Tablet hardness

Hardness was measured using a calibrated hardness tester and was recorded in kp. The means and standard deviations are presented (Table 3).

5.4. Drug release

Dissolution was carried out in an automated dissolution tester using the USP XXIII paddle assembly (apparatus II) set at 50 rpm and using 900 ml of pH 6.0 phosphate buffer. The amount of theophylline anhydrous dissolved was determined from ultraviolet absorbances at the wavelength of maximum absorbance (272 nm) of the filtered portions of the solution under test. Six tablets were tested from each batch and the mean percent drug release was calculated and plotted versus time (Fig. 5–9, see Results).

5.5. Scanning electron microscopy (SEM)

Tablets from selected batches were examined using scanning electron microscopy. The test was performed as described in step 4.3.

6. Results and discussion

6.1. Effect of manufacturing method on granule characteristics

On evaluating the granule characteristics, it was found that the Hausner ratio was not statistically different for all the batches ($p > 0.05$). The manufacturing method had no significant effect on the flowability of the granules (Table 2). Gordon et al. [13] reported that angle of repose values which are $\leq 30°$ generally indicate a free flowing material and angles $\geq 40°$ indicate poorly flowing materials. In the results presented in this study, the angles fall in the range of 31–33 ° which are on the borderline of good flow.

Ukita and Murakami [14] compared melt granulation in a high shear mixer-granulator, verus wet granulation in the fluidized bed and the high shear mixer-granulator for the preparation of essential oil loaded granules. Melt granulation was carried out in a jacket equipped high shear mixer. The jacket was heated prior to granulation by circulating hot water (75 °C). The granule properties were significantly affected by the granulation method used and also by the drying method, with the granules produced by melt granulation in the high shear and dried by jacket cooling having a high bulk density (0.67 g/ml). Fluid bed wet granulation had the lowest bulk density of 0.32 g/ml. The presented results do not agree with the above. This could be explained by the use of different starting materials. In this study, the starting material is in granular form and not fine powder to be granulated. Additionally, the amount of melt excipient applied was 10 % w/w, which was not high enough to cause a significant effect on granule characteristics.

Table 2: Effect of manufacturing method and melt excipient on granules characteristics.

Manufacturing method	Melt excipient type	Angle of repose (degrees)		Bulk density (g/ml)		Tapped density (g/ml)		Hausner ratio	
		Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
HS-HMT[a]	CSA	31.7	1.250	0.588	0.010	0.649	0.012	1.10	0.002
HS-HMT	GB	32.2	0.252	0.594	0.005	0.629	0.006	1.11	0.001
FB-HMT[b]	CSA	32.4	0.252	0.568	0.000	0.621	0.005	1.09	0.010
FB-HMT	GB	31.0	0.755	0.617	0.011	0.694	0.000	1.13	0.020
DC[c]	CSA	31.8	0.265	0.550	0.009	0.610	0.000	1.11	0.017
DC	GB	32.0	0.650	0.568	0.018	0.633	0.011	1.11	0.016

[a] High shear hot melt technique. [b] Fluid bed hot melt techniques. [c]Direct compression.

Table 3: Effect of manufacturer method, melt excipient, and compression force on tablet characteristics.

Manufacturing method	Melt excipient	CF Compression force (KN)	Weight (mg)		Thickness (mm)		Hardness (kp)	
			Mean	S.D.	Mean	S.D.	Mean	S.D.
HS-HMT[a]	CSA	4– 6	387.4	4.119	4.06	0.025	10.9	0.563
HS-HMT	CSA	9–11	378.5	5.617	3.85	0.040	10.7	0.281
HS-HMT	GB	4– 6	384.4	2.799	4.06	0.025	7.5	0.497
HS-HMT	GB	9–11	373.8	2.913	3.81	0.033	8.7	0.384
FB-HMT[b]	CSA	4– 6	382.1	3.277	4.03	0.025	8.3	0.459
FB-HMT	CSA	9–11	381.2	3.655	3.80	0.022	10.5	0.502
FB-HMT	GB	4– 6	383.0	5.812	4.05	0.036	4.5	0.408
FB-HMT	GB	9–11	377.7	3.377	3.83	0.033	6.1	0.380
DC[c]	CSA	4– 6	384.7	6.140	4.02	0.047	6.8	0.464
DC	CSA	9–11	379.2	7.455	3.81	0.050	8.8	0.888
DC	GB	4– 6	386.2	2.217	4.05	0.027	6.5	0.331
DC	GB	9–11	383.7	2.478	3.84	0.023	8.7	0.280

[a] High shear hot melt technique. [b] Fluid bed hot melt techniques. [c]Direct compression.

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Even though there were no differences in the granules physical characteristics, the scanning electron micrographs (Fig. 1 and 2) were different in their appearance. The figures demonstrated that the melt excipient droplets were just deposited on the granules in the high shear technique, whereas in the fluid bed hot melt technique, spreading of the melt excipient occurred followed by coating.

6.2. Effect of melt excipient on granule characteristics

There was no significant difference in the granule characteristics ($p > 0.05$) on evaluating the two melt excipients, when compared within each manufacturing method (Table 2).

By evaluating the application of the two melt excipients in the fluid bed technique, it was observed that at the beginning of spraying GB the difference between the actual inlet and the actual outlet temperature was about 35 °C, while at the end of the spraying process this difference decreased to about 20 °C (Fig. 3). In case of applying CSA, there was no difference at the start of spraying between the inlet and the outlet air temperatures. The maximum difference was 5 °C, and it appeared at the end of the spraying process (Fig. 4). The parameters used for coating are listed in Table 1.

For an optimum coating process, it is better to have a small difference between the inlet and the outlet air temperatures in order to get uniform heat distribution in the fluid bed chamber, and thus a homogenous coat formation. This was easier to achieve with CSA than with GB due to its lower melting point. A non-uniform distribution of the melt excipient took place in case of GB. Also, the higher melting point of GB required longer time for pre-warming the equipment and the product prior to spraying. This value was 31 min and 57 s in case of GB, and was 8 min and 52 s in case of CSA (Fig. 3 and 4).

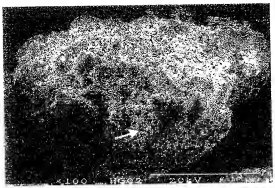

Fig. 1: Scanning electron micrograph of substrate granules coated with cetostearyl alcohol (5 % w/w). Top spray fluid bed processor (magnification × 100). The arrow points to a granule coated uniformly with the melt excipient. The melt excipient droplets are deposited in the form of thin shiny small sheets on the granule.

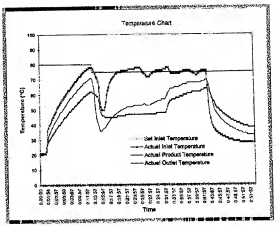

Fig. 3: Hot melt spraying process in the Glatt GPCG-1. Glyceryl behenate 10 % w/w. batch no. 98J21G79.

Fig. 2: Scanning electron micrograph of substrate granule coated with cetostearyl alcohol (5 % w/w). High shear mixer-granulator (magnification × 100). The arrow points to some melt excipient agglomerates formed upon its addition to the granules in the high shear mixer. A granulation process occurred in the high shear mixer-granulator in comparison to a coating process in the fluid bed processor.

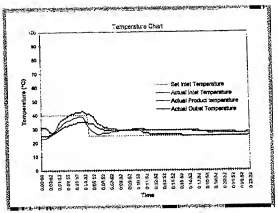

Fig. 4: Hot melt spraying process in the Glatt GPCG-1. Cetostearyl alcohol 10 % w/w, batch no. 98J8 G67.

6.3. Effect of manufacturing method on tablet hardness and drug release

CSA based tablets

At the low compression force (4–6 kN), the tablets had significantly variable hardness ($p < 0.05$), with the high shear technique producing the hardest tablets followed by fluid bed technique, and then direct compression. While at the high compression force (9–11 kN), tablets produced by the fluid bed technique were not significantly different ($p > 0.05$) from those by the high shear technique, but were harder than those produced by direct compression (Table 3). When tablets were manufactured using the hot melt technique, the granule binding was stronger during compression due to the more uniformly distributed melt excipient over the granules compared to direct compression.

Fig. 5 demonstrates that there was a significant difference in drug release between the three different methods at both compression forces used. Tablets prepared by the hot melt techniques produced slower drug release than by direct compression.

This result supports the work by Foster and Parrott [15] who prepared matrices compressed from melts of hydrogenated castor oil and a drug. The drug release was compared with that from matrices prepared by the compression of physical mixtures. The release was slower from the matrix prepared by the melt process. They concluded that the rate of drug release from matrices may be altered by the method of manufacturing.

Harder tablets exhibited a slower drug release pattern, thus it could be drawn that the drug release from CSA based tablets could be correlated to the tablet hardness.

GB based tablets

The three different manufacturing methods produced tablets with variable hardness values (Table 3). Tablets compressed at the low compression force produced using the high shear technique were the hardest followed by those produced by direct compression and then by fluid bed technique. At the high compression force, tablets manufactured by the high shear technique were not significantly different from those by the direct compression, but were harder than those produced by fluid bed technique.

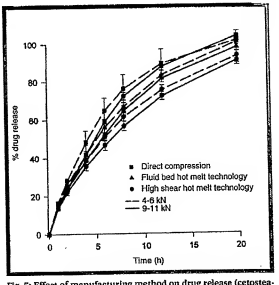

Fig. 5: Effect of manufacturing method on drug release (cetostearyl alcohol 10 %).

The results of the directly compressed tablets were different from those obtained by Meshali et al. [16] where sustained release theophylline matrix tablets were manufactured using direct compression. GB matrix tablets containing varying percentages of potassium chloride, hydroxypropylmethyl cellulose or mannitol were produced. All the formulations produced tablets with good hardness ranging between 5.5–6.4 kp. Tablets produced in this study were found to be harder (6.5–8.7 kp).

Table 4 summarizes the statistical analysis of the effect of manufacturing method on CSA and GB based tablets' hardness.

There was no difference in drug release between the tablets produced by direct compression and high shear technique. A slower release was observed for the tablets made by fluid bed technique (Fig. 6).

Table 4: Statistical analysis of the effect of manufacturing method on cetostearyl alcohol and glyceryl behenate based tablets hardness.

Comparison of manufacturing method		CSA		GBA	
		Difference between means		Difference between means	
		Low compression forces	High compression forces	Low compression forces	High compression forces
HS-HMT[a]	FB-HMT[b]	2.6300*	0.1900	2.9900*	2.6100*
HS-HMT	DC[c]	4.0900*	1.9000*	1.0100*	0.0500
FB-HMT	HS-HMT	−2.6300*	−0.1900	−2.9900*	−2.6100*
FB-HMT	DC	1.4600*	1.7100*	−1.9800*	−2.5500*
DC	HS-HMT	−4.0900*	−1.9000*	−1.0100*	−0.0600
DC	FB-HMT	−1.4600*	−1.7100*	1.9800*	2.5500*

[a] High shear hot melt technique. [b] Fluid bed hot melt techniques. [c] Direct compression. * Significant difference ($p < 0.05$).

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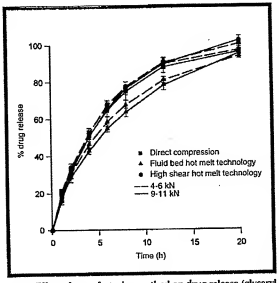

Fig. 6: Effect of manufacturing method on drug release (glyceryl behenate 10 %).

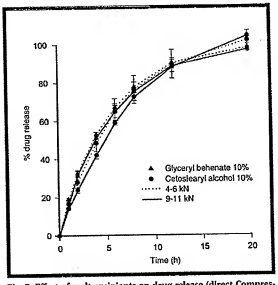

Fig. 7: Effect of melt excipients on drug release (direct Compression).

It is to be noted that the temperature of the melt excipients was maintained at 110–115 °C when applied to the substrate granules in the high shear mixer-granulator. The temperature of the granules, before applying the melt excipient, ranged between 19–21 °C. Knowing that the melting point of GB is 69–70 °C, thus upon its application it immediately congealed. This was fortified by the large difference between the melt excipients and the substrate granules' temperature. The drug release from the tablets made by the high shear technique and direct compression was not significantly different which supported the above mentioned hypothesis.

The slower release observed using the fluid bed technique could be due to better coating of the granules in view of the closeness of the product temperature to the melting point of GB, as compared to the large temperature difference in the high shear technique.

Based on the above, it is to be accentuated that, unlike CSA, GB based tablets exhibited no correlation between the tablet hardness and drug release characteristics.

6.4. Effect of compression force on tablet hardness and drug release

Increasing the compression force caused a significant increase of the hardness of both the CSA and GB based tablets manufactured by the three manufacturing methods (Table 3).

However, for both CSA and GB based tablets, there was no significant difference in drug release between tablets produced at the low (4–6 kN) and the high compression force (9–11 kN) with all the three manufacturing methods (Fig. 5 and 6). Thus the compression force had no significant effect on drug release.

These results are in agreement with the work of Bansal, Patil and Plakogiannis [17] who studied the effects of compression pressure on tablet hardness and the release from directly compressible wax-matrix tablets. Results indicated that increased compression forces resulted in harder tablets. In addition, dissolution studies indicated no significant effect of hardness on dissolution properties.

6.5. Effect of melt excipient type on tablet hardness and drug release

When tablets were produced using the fluid bed technique and the high shear technique, CSA based tablets were significantly harder than GB based tablets at both compression forces, while no significant difference was observed with directly compressed tablets (Table 3). This could be possibly explained by the lower melting point of CSA allowing more binding upon compressing the granules produced by the hot melt techniques.

There was no significant difference in drug release between CSA and GB based tablets, at both compression forces, using direct compression and fluid bed technique as manufacturing methods (Fig. 7 and 8).

Tablets containing GB as a melt excipient produced a faster drug release than those containing CSA, when manufactured using the high shear technique (Fig. 9).

The structure of the tablet matrix manufactured by the high shear technique, after placing the tablets in the dissolution medium (phosphate buffer pH 6.0) for 2 h, was examined using scanning electron microscopy (Fig. 10 and 11). The CSA based tablets showed pores through which the drug diffused to the dissolution medium, while the GB based tablets showed cracks in the tablets causing the dissolution rate to be faster. This could be due to the premature congealing of the GB

prior to reaching the granules as explained earlier in step 6.3. This did not occur with CSA since it has a lower melting point range of 39–49 °C giving more chance for the wax to spread on the granules before congealing.

7. Conclusions

Hot melt technology was evaluated as a futuristic method for manufacturing modified release solid dosage forms. Hot melt technology was evaluated in the top spray fluid bed processor and the high shear mixer/granulator in comparison to direct compression. To accomplish this goal, proper selection of process and formulation variables was substantial.

Granules consisting of theophylline monohydrate and lactose granulated with polyvinylpyrrolidone were used as substrate. The lipophilic modified release melt excipients, CSA and GB, were evaluated.

The resulting granules and tablets were examined using scanning electron microscopy (SEM), and were evaluated for their physical characteristics. In vitro dissolution tests were done using automated USP apparatus II, at a paddle speed of 50 rpm in 900 ml pH 6.0 phosphate buffer for 20 h.

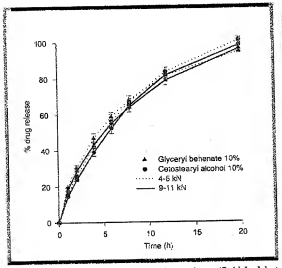

Fig. 8: Effect of melt excipients on drug release (fluid bed hot melt technique).

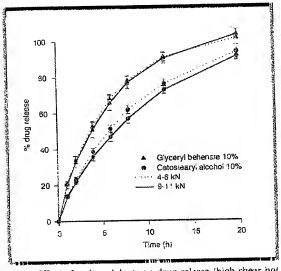

Fig. 9: Effect of melt excipients on drug release (high shear hot melt technique).

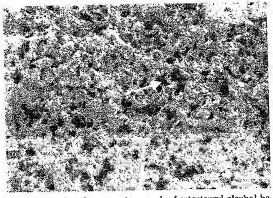

Fig. 10: Scanning electron micrograph of cetostearyl alcohol based tablets (10 % w/w) after 2 h of dissolution. High shear mixer-granulator (magnification × 30). The figure demonstrates a porous tablet matrix consisting of an insoluble non disintegrating waxy system. The arrow points to one of the holes in the tablet matrix. The holes in the matrix are formed due to the penetration of the dissolution medium into the tablet resulting in leaching of the drug and the water soluble excipients. The drug which was present on the tablet surface dissolved directly into the medium while the drug inside the tablet core diffused through the tablet matrix first before it reached the tablet outer surface.

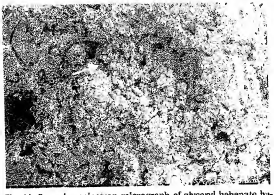

Fig. 11: Scanning electron micrograph of glyceryl behenate based tablets (10 % w/w) after 2 h of dissolution. High shear mixer-granulator (magnification × 30). The figure demonstrates a non coherent tablet matrix after placing the tablet in the dissolution medium. The arrow points to holes in the matrix through which the drug has diffused. It was also observed that the tables eroded during dissolution, which in turn caused a significantly faster drug release rate due to the continuous exposure of the drug to the dissolution medium together with the holes and cracks in the tablet matrix.

It was found that hot melt technology significantly extended the release of theophylline from the resulting tablets compared to those manufactured by direct compression. This depended on the melt excipient type and the method of application. The drug release from CSA based tablets (10 % w/w) was the slowest in case of the high shear hot melt technique. The release from tablets manufactured by the fluid bed technique and direct compression was faster. Tablets based on GB (10 % w/w) showed a significantly slower drug release when produced by the fluid bed technique compared to those produced by the high shear technique and direct compression.

CSA based tablets had superior tablet properties than GB based tablets. CSA based tablets produced using the hot melt technology were significantly harder than those produced by direct compression. In case of GB, the hardest tablets were produced using the high shear technique, followed by direct compression. The fluid bed technique produced the weakest tablets.

From the qualitative subjective point of view, using the same amount of material, direct compression was as successful as the high shear technique in modifying drug release in case of GB, and almost as the fluid bed technique in case of CSA.

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Correspondence:
Prof. Dr. Adel Sakr,
Industrial Pharmacy Graduate Program,
College of Pharmacy, University of Cincinneti,
3223 Eden Avenue, Cincinnati,
OH 45267-0004 (USA),
e-mail: Adel.Sakr@uc.edu